

WHAT IS CLAIMED IS:

1. A method for identifying nucleotides at one or more base positions in a plurality of target nucleic acids molecules, comprising:
synthesizing extension products of the target nucleic acid in the
5 presence of chain terminating nucleotides and mass-matched nucleotides;
determining the mass of each extension product; and
calculating a mass shift from a period for the mass of each extension product,
whereby the nucleotides in the target nucleic acid molecules are
10 identified by determining the nucleotide that corresponds to each mass shift.
2. The method of claim 1, wherein the mass-matched deoxy-nucleotides are identical.
3. The method of claim 1, wherein a mass-matched deoxy-
15 nucleotide is deoxyinosine, 5-nitroindole, 3-nitropyrrole , 3-methyl
7-propynyl isocarbostyryl, 5-methyl isocarbostyryl or 3-methyl
isocarbostyryl.
4. A kit for determining the sequence of a target nucleic acid, comprising mass-matched nucleotides.
- 20 5. A kit for determining the sequence of a target nucleic acid, comprising pair-matched nucleotides and mass-matched chain terminating nucleotides.
6. A kit for determining the sequence of a target nucleic acid, comprising pair-matched nucleotides and chain terminating nucleotides
25 that form base pairs of distinct molecular weight, and optionally including instructions for sequencing using these reagents.
7. A kit for determining the sequence of a target nucleic acid, comprising pair-matched nucleotides and mass-labeled primers, and optionally including instructions for sequencing using these reagents.

8. A computer-based method for identifying nucleotide or nucleotides at one or more base positions in a target nucleic acid molecule or plurality thereof, comprising:

5 a) entering a computer, a primer sequence or primer mass, a mass of an individual mass-matched deoxynucleotide and the identify of chain terminators used;

b) entering the masses of the fragments generated by a primer extension reaction, wherein the primer is extended by mass-matched deoxynucleotides;

10 c) determining P_{base} , wherein P_{base} is the base periodicity in daltons;

d) calculating $M_{diff}[n]$ for each nucleotide base to be identified, wherein:

$$M_{diff}[n] = M_{obs}[n] - M_{PR}[n];$$

$$M_{PR}[n] = (M_{primer} + M_{light}) + (n - 1) P_{base};$$

15 $M_{obs}[n]$ is the observed peak;

where:

n is the base position;

$M_{PR}[n]$ is the n^{th} periodic reference mass;

M_{primer} is the mass of the primer;

20 M_{light} is the mass of the lightest nucleotide terminator;

and

e) determining the identity of a nucleotide at any base position or the positional mass difference by determining $M_{diff}[n]$ and comparing it to a database of previously calculated values of M_{diff} for each of the chain
25 terminating nucleotides.

9. A system for high throughput analysis of nucleic acid samples, comprising:

a processing station that performs a chain extension reaction, in the presence of mass-matched nucleic nucleotides, on a nucleic acid
30 sample in a reaction mixture;

a robotic system that transports the resulting products from the processing station to a mass measuring station, wherein the masses of the products of the reaction are determined; and

- 5 a data analysis system that processes the data from the mass measuring station and that is programmed to perform the method of claim 46 to identify a nucleotide or nucleotides at one or more base positions in nucleic acid molecule in the sample.

10. The system of claim 10, further comprising a control system that determines when processing at each station is complete and, in response, moves the sample to the next test station, and continuously processes samples one after another until the control system receives a stop instruction.

11. The system of claim 10, wherein the mass measuring station is a mass spectrometer.